

REMARKS

Following entry of this amendment, claims 41 to 51 are pending in the application. Claims 1 to 40 have been canceled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of those claims in the future. Claims 41 to 51 have been added. Support for new claims 41 to 44, 49, and 50 can be found in the specification, e.g., at page 5, lines 25 to 28; at page 17, lines 15 to 20; and at page 28, lines 22 to 26. Support for new claim 45 can be found in the specification, e.g., at page 16, lines 23 to 25. Support for new claims 46 to 48 can be found in the specification, e.g., at page 22, lines 7 to 8. Support for new claim 51 can be found in the specification, e.g., at page 28, lines 22 to 26; and at page 16, lines 23 to 25. Claims 41 to 51 add no new matter.

Terminal Disclaimer

Applicants filed a Terminal Disclaimer over U.S. Application No. 11/192,885 on November 27, 2007. Applicants file herewith a petition to withdraw the Terminal Disclaimer over the '885 application. The '885 application has been abandoned. Thus, withdrawal of the Terminal Disclaimer should not result in reassertion of the obviousness-type double-patenting rejection over the '885 application.

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 29 to 40 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,441,038 (Loder) in view of U.S. Publication

No. US 2002/0086864 (Wong). Action at page 2. Specifically, the Examiner contended that

Loder et al teach that chronic fatigue syndrome, fibromyalgia and perceptive pain associated therewith and depressed mood as known disorders of neurological origin is treatable with a drug that 'is a compound which inhibits both noradrenaline and serotonin reuptake' (Col. 9, lines 7-9) and more specifically, **milnacipran accompanied by either L-phenylalanine or tyrosine** (Col. 9, lines 17-32, claims 1-4).

Id. (emphasis added). The Examiner stated that Loder does not teach "dosage escalation as claimed instantly for treating fibromyalgia." *Id.* at page 3. The Examiner alleged that Wong teaches a method of treating fibromyalgia wherein "the physician or psychiatrist could employ relatively low dosages at first, subsequently increasing the dose until a maximum response is obtained ([0057])." *Id.* The Examiner contended that "it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to optimize the dosage amount based on the teachings of Wong et al. teaching that the dosage can be increased by small increments until the optimum effect is achieved." *Id.* at page 4.

Applicants respectfully traverse. Claims 29 to 40 have been canceled without prejudice or disclaimer. Claims 41 to 51 have been added. Claim 41 recites:

41. A method of treating fibromyalgia, the method consisting essentially of administering to a patient in need thereof an active ingredient, wherein the active ingredient is selected from milnacipran, or a pharmaceutically acceptable salt thereof, or milnacipran and a pharmaceutically acceptable salt thereof, and wherein the administering comprises:

administering a first dosage amount of the active ingredient of up to 100 mg per day for a first period of time,

administering a second dosage amount of the active ingredient of about 1.5 to 2.5 times greater than the first dosage amount for a second period of time,

administering a third dosage amount of the active ingredient of about 1.5 to 2.5 times greater than the second dosage amount for a third period of time, and
administering a fourth dosage amount of the active ingredient of about 1.5 to 2.5 times greater than the third dosage amount for a fourth period of time.

(Emphasis added.) Claims 42 to 51 ultimately depend from claim 41.

To establish a *prima facie* case of obviousness, there must be some reason for one skilled in the art to modify a document or combination of documents to arrive at the claimed invention. See, e.g., MPEP § 2143. The mere fact that a document can be modified does not render the resulting modification obvious unless the results would have been predictable to one of ordinary skill in the art. See MPEP § 2143.01(III) (citing *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007)). Furthermore, when the prior art teaches away from making a particular modification, that modification is more likely to be nonobvious. See, e.g., *KSR Int'l Co.*, 82 USPQ2d at 1395.

As noted by the Examiner, Loder discusses a method involving administration of a noradrenaline reuptake inhibitor *in combination with* a noradrenaline precursor such as phenylalanine or tyrosine. Applicants assert that the language “the method consisting essentially of” in claim 41 excludes methods in which milnacipran is administered with another active ingredient. One skilled in the art would have had *no reason* to remove the noradrenaline precursor from Loder’s combinations. Loder expressly teaches that administering a noradrenaline reuptake inhibitor in the absence of a noradrenaline precursor is much less effective than the combination. In fact, Loder *teaches away* from using a noradrenaline reuptake inhibitor alone by proposing a specific mechanism to explain why the combinations are so much more effective. Thus, as will be explained below, applicants assert that Loder would have failed to render

obvious the use of a noradrenaline reuptake inhibitor *in the absence* of a noradrenaline precursor.

One skilled in the art would have had no reason to use a noradrenaline reuptake inhibitor in the absence of a noradrenaline precursor based on Loder

As noted above, claim 41 excludes methods in which milnacipran is administered with an additional active ingredient. Loder, however, only discusses a method involving administration of a noradrenaline reuptake inhibitor in combination with a noradrenaline precursor such as phenylalanine or tyrosine. Specifically, Loder is directed to

[a] method of treatment of disorders of neurological origin and drug formulations for use in the method. . . . The treatment comprises administering to a patient in need thereof **a selective inhibitor of noradrenaline reuptake combined with either phenylalanine or tyrosine** in the same dosage formulation or the same pack.

See Abstract (emphasis added).

Throughout the specification, Loder emphasizes that it is the combination of noradrenaline reuptake inhibitors with noradrenaline precursors that is the subject of the invention. Loder discusses, for example, “[o]ther drugs which are effective **in combination with** phenylalanine or tyrosine are drugs which are combined inhibitors of both noradrenaline and serotonin uptake....” Col. 1, lines 42 to 44 (emphasis added). Loder also discusses a “list of possible uses **of the combinations...**” (col. 1, line 50 (emphasis added)) and “[a] particularly important new use **for the combinations...**” (col. 1, lines 57 to 58 (emphasis added)).

In assessing the effectiveness of the combinations, Loder indicates that

[t]he anecdotal evidence indicating that **noradrenaline precursors and noradrenergic drugs** like lofepramine and desipramine are particularly effective, and the new and unexpected clinical trial evidence which clearly proves efficacy.... In particular, **the combination of** noradrenaline

precursors, phenylalanine and tyrosine, coupled with a drug which either has its sole action or a component of its action the inhibition of noradrenaline reuptake, is now seen to be valuable in the treatment of fatigue in any form, in the management of rehabilitation after stroke, in the treatment of stress in any form, and in the treatment of fibromyalgia and related disorders such as irritable bowel syndrome.

Col. 3, lines 13 to 28 (emphasis added). Loder further asserts the combination of a noradrenaline reuptake inhibitor with a noradrenaline precursor is specifically responsible for that effectiveness:

These effects of noradrenergic compounds alone are important but relatively modest. **Our concept of combining** a noradrenergic drug like lofepramine or desipramine, together with a noradrenaline precursor such as phenylalanine or tyrosine, **is much more effective.**"

Col. 6, lines 36 to 40 (emphasis added).

Thus, based on the teachings of Loder, one skilled in the art would have had *no reason* to administer milnacipran in the absence of a noradrenaline precursor.

Loder explicitly teaches away from the use of a noradrenaline reuptake inhibitor in the absence of a noradrenaline precursor

Not only would one skilled in the art have had no reason to modify Loder by removing the noradrenaline precursor required for the effectiveness of his combinations, Loder goes even further - he teaches away from the claimed invention in his explanation of the mechanism of action of the combinations. Specifically, to explain his observations, Loder proposes a mechanism that requires the combined effect of increasing noradrenaline synthesis and decreasing noradrenaline uptake. See col. 6, lines 56 to 66. According to Loder, that mechanism

...is the explanation **for the strong interaction** we have observed between lofepramine and phenylalanine. In MS, the LC and LT noradrenergic systems are activated and stressed leading to loss of the feedback control of noradrenaline synthesis. As a result **phenylalanine can enhance noradrenaline synthesis and strongly interact with**

lofepramine which inhibits uptake of released noradrenaline and so activates noradrenergic systems.

Col. 6, line 62, to col. 7, line 3 (emphasis added). Furthermore, according to Loder, the described combinations had not previously been proposed because the mechanism was not appreciated:

Because of a failure to understand this unique mechanism, although it has been proposed that phenylalanine and tyrosine may be used to treat depression, **it has never been proposed that phenylalanine or tyrosine should be specifically combined with drugs which have specific effects on noradrenaline reuptake** such as lofepramine, desipramine and reboxetine. Such combinations will be particularly effective in treating depression, especially when that depression is associated with chronic stress and abnormal function of the LC and LT systems.

Col. 7, l. 61, to col. 8, l. 3 (emphasis added).

Finally, Loder provides a clinical example that teaches that noradrenaline reuptake inhibitors used alone are ineffective for treating fibromyalgia and chronic fatigue syndrome. In Case History No. 1, Loder describes a 41 year old woman who had suffered from chronic fatigue syndrome associated with fibromyalgia and irritable bowel syndrome for 12 years. See col. 5, lines 39 to 65. According to Loder,

[s]he was given almost all conceivable treatments over the years including ... noradrenaline reuptake inhibiting antidepressants.... Some of these treatments produced transient effects but these never lasted. **She was then given combined treatment** with lofepramine, 70 mg bd and L-phenylalanine, 500 mg bd. Over a period of 2-3 weeks she experienced a considerable improvement in fatigue, in fibromyalgia and in her irritable bowel.... **After six months she was essentially back to her normal self."**

Id., lines 53 to 65 (emphasis added).

Thus, applicants assert that Loder's invention is based on his "unique mechanism," which dictates the use of a noradrenaline precursor in combination with a noradrenergic drug. In fact, Loder's Case History No. 1 specifically teaches that

noradrenergic drugs used alone are ineffective. Thus, Loder teaches away from a method that involves administering a noradrenaline reuptake inhibitor in the absence of a noradrenaline precursor.

In sum, considering Loder, one skilled in the art would have had no reason to modify Loder's combinations by removing the noradrenaline precursor, and furthermore, Loder explicitly teaches away from making such a modification. Accordingly, Loder would have failed to render obvious a method involving administering a noradrenaline reuptake inhibitor in the absence of a noradrenaline precursor.

Applicants assert that Wong would have failed to remedy the deficiencies of Loder. That is, Wong would have given one skilled in the art no reason to remove the required noradrenaline precursor from the combinations of Loder. Because Wong would have failed to remedy the deficiencies of Loder, applicants need not address the Examiner's contentions with respect to Wong and certain elements of the claims. By not addressing those contentions, applicants in no way acquiesce to them.

In conclusion, applicants assert that the combination of Loder and Wong would not have rendered the pending claims obvious for at least the reasons discussed above. Applicants therefore respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Loder in view of Wong.

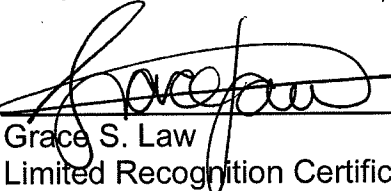
Applicants respectfully assert that the present application is in condition for allowance and request that the Examiner issue a timely Notice of Allowance.

Please grant any extensions of time required to enter this Amendment and
Response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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By: 

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